

## Derivation and Characterization of Myeloproliferative Disorder Stem Cells from Human ES Cells

### Grant Award Details

Derivation and Characterization of Myeloproliferative Disorder Stem Cells from Human ES Cells

**Grant Type:** New Faculty II

**Grant Number:** RN2-00910

**Project Objective:** Project seeks to identify critical leukemia stem cell survival and self-renewal factors. Two critical factors being studied are BCR-ABL and JAK-2 which are key drivers of myeloproliferative disorders.

**Investigator:**

**Name:** Catriona Jamieson

**Institution:** University of California, San Diego

**Type:** PI

**Disease Focus:** Blood Cancer, Cancer

**Human Stem Cell Use:** Cancer Stem Cell, Embryonic Stem Cell

**Award Value:** \$3,065,572

**Status:** Closed

### Progress Reports

**Reporting Period:** Year 1

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## Grant Application Details

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**Application Title:** Derivation and Characterization of Myeloproliferative Disorder Stem Cells from Human ES Cells

**Public Abstract:** Cancer is the leading cause of death for people younger than 85. High cancer mortality rates related to resistance to therapy and malignant progression underscore the need for more sensitive diagnostic techniques as well as therapies that selectively target cells responsible for cancer propagation. Compelling studies suggest that human cancer stem cells (CSC) arise from aberrantly self-renewing tissue specific stem or progenitor cells and are responsible for cancer propagation and resistance to therapy. Although the majority of cancer therapies eradicate rapidly dividing cells within the tumor, the rare CSC population may be quiescent and then reactivate resulting in disease progression and relapse. We recently demonstrated that CSC are generated in chronic myeloid leukemia by activation of beta-catenin, a gene that allows cells to reproduce themselves extensively. However, relatively little is known about the sequence of events responsible for leukemic transformation in more common myeloproliferative disorders (MPDs) that express an activating mutation in the JAK2 gene. Because human embryonic stem cells (hESC) have robust self-renewal capacity and can provide a potentially limitless source of tissue specific stem and progenitor cells, they represent an ideal model system for generating and characterizing human MPD stem cells. Thus, hESC cell research harbors tremendous potential for developing life-saving therapy for patients with cancer by providing a platform to rapidly and rationally test new therapies that specifically target CSC. To provide a robust model system for screening novel anti-CSC therapies, we propose to generate and characterize BCR-ABL<sup>+</sup> and JAK2<sup>+</sup> MPD stem cells from hESC. We will investigate the role of genes that are essential for initiation of these MPDs such as BCR-ABL and JAK2 V617F as well as additional mutations in beta-catenin or GSK3 $\beta$  implicated in CSC propagation. The efficacy of a selective BCR-ABL and JAK2 inhibitors at blocking BCR-ABL<sup>+</sup> and JAK2<sup>+</sup> human ES cell self-renewal, survival and proliferation alone and in combination with a potent and specific beta-catenin antagonist will be assessed in robust in vitro and in vivo assays with the ultimate aim of developing highly active anti-MPD stem cell therapy that may halt progression to acute leukemia and obviate therapeutic resistance.

**Statement of Benefit to California:**

Although much is known about the genetic and epigenetic events involved in CSC production in a Philadelphia chromosome positive MPD like chronic myeloid leukemia (CML), comparatively little is known about the molecular pathogenesis of the five-fold more common Philadelphia chromosome negative (Ph-) MPDs. MPD patients have a moderately increased risk of fatal thrombotic events as well as a striking 36-fold increased risk of death from transformation to acute leukemia. Recently, a point mutation, JAK2 V617F(JAK2+), resulting in constitutive activation of the JAK2 cytokine signaling pathway was discovered in a large proportion of MPD patients. A critical barrier to developing potentially curative therapies for both BCR-ABL+ and JAK2+ MPDs is a comprehensive understanding of relative contribution of BCR-ABL and JAK2 V617F to disease initiation versus transformation to acute leukemia. We recently discovered that JAK2 V617F is expressed at the hematopoietic stem cell level in PV, ET and MF and that JAK2 skewed differentiation in PV is normalized with a selective JAK2 inhibitor, TG101348. However, a detailed molecular pathogenetic characterization has been hampered by the paucity of stem and progenitor cells in MPD derived blood and marrow samples. Because hESC have robust self-renewal capacity and can provide a potentially limitless source of tissue specific stem and progenitor cells in vitro, they represent an ideal model system for generating human MPD stem cells. Thus, California hESC research harbors tremendous potential for understanding the MPD initiating events that skew differentiation versus events that promote self-renewal and thus, leukemic transformation. Moreover, a more comprehensive understanding of primitive stem cell fate decisions may yield key insights into methods to expand blood cell production that may have major implications for blood banking. Clinical Benefit Generation of MPD stem cells from hESC would provide an experimentally amenable and relevant platform to expedite the development of sensitive diagnostic techniques to predict disease progression and to develop potentially curative anti-CSC therapies. Economic Benefit The translational research performed in the context of this grant will not only speed the delivery of innovative MPD targeted therapies for Californians, it will help to train California's future R&D workforce in addition to developing leaders in translational medicine. This grant will provide the personnel working on the project with a clear view of the importance of their research to cancer therapy and a better perspective on future career opportunities in California as well as directly generate revenue through development and implementation of innovative therapies aimed at eradicating MPD stem cells that may be more broadly applicable to CSC in other malignancies.

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